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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/489,760	01/21/2000	Elsa A. J. M. Goulmy	4285us	6225

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/489,760	Applicant(s) GOULMY ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11/4/02 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *Five* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): *See Continuation Sheet*.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *None*.

Claim(s) objected to: *None*.

Claim(s) rejected: *1-5 and 20-24*.

Claim(s) withdrawn from consideration: *None*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 3. Applicant's reply has overcome the following rejection(s):

The rejection of Claims 1-5, 9 and 20-24 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention (New matter) is hereby withdrawn in view of the proposed claims 1, 2 and cancelation of claim 9.

The rejection of Claims 1-5, 9 and 20-24 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is hereby withdrawn in view of the proposed claims 1, 2 and cancelation of claim 9.

The rejection of Claims 1-2, 4-5, 9, 21 and 23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Haan et al (of record, Eur J Immunol 26:2680-2685, 1996; PTO 892) is hereby withdrawn in view of the proposed claims 1, 2 and cancelation of claim 9.

Continuation of 5. does NOT place the application in condition for allowance because:

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a peptide having up to 15 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide consisting the seuqence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine or an arginine residue, (2) an immunogenic polypeptide having up to 15 amino acids obtainable from the minor Histocompatibility antigen HA-1, said immunogenic polypetpdie consisting of the sequence VLXDDLLEA (SEQ ID NO: 1) wherein X represents a histidine or an arginine residue for diagnosing minor Histocompatibility antigen (HA-1) incompatibility between donor and recipient of bone marrow transplant using in vitro CTL assays (See pages 5, 7, 14-17, 25-26 of the specification), generation of VLHDDLLEA or VLRDDLLEA specific CTL in vitro for adoptive immunotherapy, does not reasonably provide enablement for (1) any "vaccine" or any "pharmaceutical formulation" comprising the peptide peptide having up to 15 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide consisting the seuqence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine or an arginine residue or an immunogenic polypeptide having up to 15 amino acids obtainable from the minor Histocompatibility antigen HA-1, said immunogenic polypetpdie "comprising" the sequence VLXDDLLEA (SEQ ID NO: 1) wherein X represents a histidine or an arginine residue for preventing any graft versus host disease or to treat any HA-1 related autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in Paper No 17.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.
The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein the peptides having a structure of nine amino acids in length for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant and generating HA-1 specific CTLs ex-vivo.
Other than the specific peptides mentioned above for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant and ex-vivo generated HA-1 specific CTLs, the specification does not teach how to make and use any peptide, any immunogenic polypeptide "having up to 15 amino acids" constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1 "comprising" the sequence VLXDDLLEA of SEQ ID NO: 1 having similar functional or immunological properties, wherein X represents a histidine or an arginine residue for a "vaccine" or a "pharmaceutical formulation" for treating any disease. The term "comprising" is open-ended. It expands the peptide, and polypeptide to include additional amino acid at either or both ends of SEQ ID NO: 1. There is insufficient guidance as to the undisclosed amino acid to be added to said peptide or immunogenic polypeptide. Further, the term "up to 15 amino acids" expands the claimed peptide of Class I to read on MHC class II peptide. Given the indefinite number and type of additional amino acids, in addition to the amino acids which already recited in SEQ ID NO: 1, it is unpredictable which undisclosed peptide and polypeptide would have the same structure and function as the claimed peptide of SEQ ID NO: 1, much less for a vaccine or pharmaceutical formulation for preventing any disease.
Abbas et al (of record) teach that even a single amino acid differences in the peptide fails to bind to the T cell receptor or loss of T cell function or both (See page 130, Table 6-7, in particular). Likewise, even a single amino acid differences in the nanomeric peptide can have a drastic effect on binding as evidence by applicants' data (see Figure 4, in particular). Because of the indefinite number of amino acids that may be encompassed in the polypeptide of instant claims and there is no disclosure about the structure associated with functions of any polypeptide, it is not clear a polypeptide "comprising" SEQ ID NO: 1 would have similar functional or immunological properties as SEQ ID NO: 1.
Colman et al (of record) teach that even a single amino acid difference in an antigen can abolish the antibody-antigen interaction entirely (page 33, in particular). Given the lack of guidance and in vivo working examples, predicting what changes can be made to the

peptide of SEQ ID NO: 1 that after insertion will retain both structure and have "similar immunological function" is unpredictable. With regard to a "vaccine" or a "pharmaceutical formulation" comprising the undisclosed peptide or the undisclosed immunogenic polypeptide mentioned above, a "vaccine" by definition is a composition to induce a specific immunity that prevent or protect against a specific disease caused by a specific agent (See Fundamental Immunology, second edition, pages 987-988, in particular). One of the criteria for a vaccine is the levels of antibody (humoral immune response) before and after immunization and the success of vaccination is judged by the extent of increase in the level of HA-1 peptide specific antibody. The second criterion for a vaccine is the ability to induce tolerance in the HA-1 negative donor and thereby protect the HA-1 positive recipient upon receiving the organ from Graft versus host disease or induction of tolerance in the HA-1 negative recipient. A vaccine and/or a "pharmaceutical formulation" in the absence of in vivo data is unpredictable because (1) the peptide/polypeptide may be inactivated before producing an effect due to proteolytic degradation or immunological inactivation or the inherently short half-life of the peptide/polypeptide; (2) the peptide/polypeptide may not bind to the TCR, or may not reach the target area because, i.e. the peptide/polypeptide may not be able to cross the mucosa or the peptide/polypeptide may be adsorbed by fluids, cells and tissues where the peptide/polypeptide has no effect; and (3) other functional properties, known or unknown, may make the peptide/polypeptide unsuitable for in vivo therapeutic use, i.e. such as adverse side effects which prohibit the use of the peptide for inhibiting Graft versus host disease. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Since there is no in vivo working examples in the specification as filed to demonstrate the effectiveness of using any peptide for preventing GVH, or treating HA-1 related autoimmune disease, it is not clear that a vaccine or a "pharmaceutical formulation" against Graft versus host disease treating HA-1 related autoimmune disease comprising said immunogenic peptide is enabled. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.
In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/4/02 have been fully considered but are not found persuasive.
Applicants' position is that (1) applicants have amended claim 1 and 2 and canceled 9. (2) the term "up to 15 amino acids" can be found on page 6, lines 27-32 of the specification. (3) the as filed specification discloses a connotation of how to use the peptides of the present invention as a vaccineation or pharmaceutical formulation (See page 7, line 25 through 8, line 25 of specification) the modes of administering vaccines and pharmaceutical formulations are well known in the art and therefore claims 4, 5 and 21-24 are enabled.

The proposed claims 1 and 2 and the cancelation of claim 9 do not overcome the enablement rejection of under 35 U.S.C. 112, first paragraph because there is insufficient guidance as to the undisclosed amino acid redidues to be added to the peptide or immunogenic polypeptide of SEQ ID NO: 1, much less for preventing any specific disease. A vaccine and/or a "pharmaceutical formulation" in the absence of in vivo data is unpredictable because (1) the peptide/polypeptide may be inactivated before producing an effect due to proteolytic degradation or immunological inactivation or the inherently short half-life of the peptide/polypeptide; (2) the peptide/polypeptide may not bind to the TCR, or may not reach the target area because, i.e. the peptide/polypeptide may not be able to cross the mucosa or the peptide/polypeptide may be adsorbed by fluids, cells and tissues where the peptide/polypeptide has no effect; and (3) other functional properties, known or unknown, may make the peptide/polypeptide unsuitable for in vivo therapeutic use, i.e. such as adverse side effects which prohibit the use of the peptide for inhibiting Graft versus host disease. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Claims 1-5 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein the peptides having a structure of nine amino acids in length for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant and generating HA-1 specific CTLs ex-vivo. The specification discloses only MHC class I peptides which are 9 amino acids in length.

The specification does not reasonably provide a written description of (1) any peptide, (2) any immunogenic polypeptide, having up to 15 amino acids constituting a T cell epitope obtainable from minor Histocompatibility antigen HA-1, said peptide "comprising" the sequence of SEQ ID NO: 1, wherein X represents a histidine or arginine, (3) any "vaccine" (4) any "pharmaceutical formulation" comprising said peptide or immunogenic polypeptide for preventing graft versus host disease or to treat any HA-1 related autoimmune disease.

There is inadequate written description about the structure associated with function of any peptide and immungenic polypeptide having up to 15 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide comprising the sequence of VLXDDLLEA (SEQ ID NO: 1) whrein X represents a histidine or an arginine residue, much less a vaccine or pharmaceutical formulation comprising said peptide or immunogenic polypeptide for prenventing or treating any disease.

Given the lack of a written description of any additional representative species of peptide or immunogenic polypeptide, a vaccine or a pharmaceutical formulation comprising said peptide, immunogenic polypeptide, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.
Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/4/02 have been fully considered but are not found persuasive.
Applicants' position is that (1) applicants have amended claim 1 and 2 and canceled 9. (2) the term "up to 15 amino acids" can be found on page 6, lines 27-32 of the specification. (3) the as filed specification discloses a connotation of how to use the peptides of the present invention as a vaccineation or pharmaceutical formulation (See page 7, line 25 through 8, line 25 of specification) the modes of administering vaccines and pharmaceutical formulations are well known in the art and therefore claims 4, 5 and 21-24 are enabled.

The proposed claims 1 and 2 and the cancelation of claim 9 do not overcome the written description rejection of under 35 U.S.C. 112, first paragraph because there is inadequate written description about the structure associated with function of any peptide and immungenic polypeptide having up to 15 undisclosed amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide comprising the seuqence of VLXDDLLEA (SEQ ID NO: 1) whrein X represents a histidine or an arginine residue, much less a vaccine or pharmaceutical formulation comprising the undisclosed peptide or immunogenic polypeptide for prenventing or treating any disease.

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